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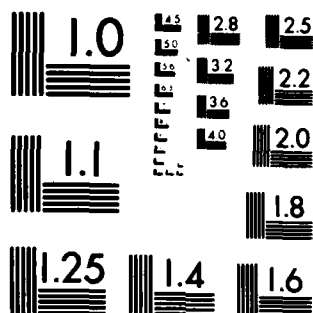
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**THE EFFECT OF WR 149024 ON SURVIVAL FOLLOWING HEMORRHAGE
IN CONSCIOUS RATS**

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DECEMBER 1983

**LETTERMAN ARMY INSTITUTE OF RESEARCH
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The Effect of WR 149024 on Survival Following Hemorrhage in Conscious Rats
--Brown and Bellamy

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THE EFFECT OF WR 149024 ON SURVIVAL FOLLOWING HEMORRHAGE IN CONSCIOUS RATS

Stopping hemorrhage is probably the most effective treatment for the combat casualty, before the soldier can be evacuated to a definitive care facility. If an antishock drug were available that could be given easily to battlefield casualties, it would be acclaimed as a major military medicine achievement. The experimental drug WR 149024 (1,18,-diamino-6,13,-diaz-9,10,-dithiaoctadecane tetrahydrochloride), an aliphatic sulfur-containing compound and alpha receptor antagonist (1,2), developed at Walter Reed Army Institute of Research, Washington, DC, enhances cardiovascular function following hemorrhage and reinfusion of the shed blood (3). According to Caldwell and Demaree (3), this drug increases cardiac output, whole blood and plasma volume, and survival, but reduces peripheral resistance in hemorrhaged and reinfused anesthetized dogs and monkeys. Under battlefield conditions, blood transfusions or other blood volume replacements are impractical therapies for the exsanguinated casualty. Consequently, we investigated the effect of WR 149024 on survival in the conscious, noninfused, hemorrhaged rat. Since the rat can tolerate rapid removal of large quantities of blood, it is an excellent model for studying severe hemorrhage. Our findings in this species are not consistent with the data reported by Caldwell and Demaree (3).

METHODS

Animals

Male, Sprague-Dawley rats, weighing 250-325 g, were used in this study. They were maintained at 23°C on a 12-hour light:12-hour dark photoperiod, fed Purina Rat Chow ad libitum and given tap water freely.

Surgery

Rats were anesthetized with Innovar-Vet (0.1 cc/100 gram body weight) given intraperitoneally (IP) and the left carotid artery was exposed surgically. A Micro-Renathane catheter (nonthrombogenic polyurethane tubing) was advanced up to 3 cm into the carotid artery, toward the heart. The catheter was held in place by a ligature around the carotid artery proximal to the insertion site. In addition, the catheter was sutured to the surrounding muscle and exteriorized on the dorsal surface of the neck. The wound was closed with stainless steel clips and the animals were allowed to recover 4-5 days before experimental use.

Hemorrhage

The amount of blood withdrawn from each rat was 30.5 ml/kg body weight. This amount is estimated to be 50% of the total blood volume (4). The carotid catheter was flushed with 0.1 cc of heparin (1000 units/ml) and connected to a peristaltic pump. The conscious rats were bled according to a logarithmic continuous bleeding schedule over a one-hour period (Table 1).

Table 1. Exponential Continuous Bleeding Scheme

First 10%	-----9.0 minutes, of the total estimated blood volume is withdrawn over
Second 10%	-----10.2 minutes,
Third 10%	-----11.6 minutes,
Fourth 10%	-----13.4 minutes,
Fifth 10%	-----15.8 minutes.

| TOTAL: 50% | -----60.0 minutes. |

Drug Treatment

At approximately 30 minutes into the hemorrhage, when 30% of the blood volume had been shed, WR 149024 lot AG was given IP; 20 rats received 5.0 mg/kg WR 149024 and 13 rats were administered 50.0 mg/kg WR 149024. The volume of each injection (in milliliters) equaled body weight $\times 10^{-3}$. Control rats (n=18) were injected with an equivalent volume of water.

Data Analysis

Following hemorrhage, survival was monitored for at least 72 hours. Survival curves were constructed for each dose, and the data analyzed by using chi square, Fisher's exact test, and a survival distribution analysis.

RESULTS

Figure 1 depicts the survival curves for controls and rats administered 5.0 or 50.0 mg/kg WR 149024 IP. Substantial increases in mortality followed both WR 149024 treatments, as compared to controls. A chi square analysis indicated that significant differences in survival did exist among the three groups ($p=0.0176$). By using Fisher's exact test, significant differences in survival were found between each drug treatment when compared with controls. Rats treated with WR 149024, either 5.0 or 50.0 mg/kg, showed a significant decrease in survival (i.e., significant increase in mortality) when compared with the water-injected controls ($p=0.0205$ and $p=0.0209$, respectively). No statistical significance was found between the WR 149024 treatments. A survival distribution analysis demonstrated that no differences existed among the times of death for each treatment and control group.

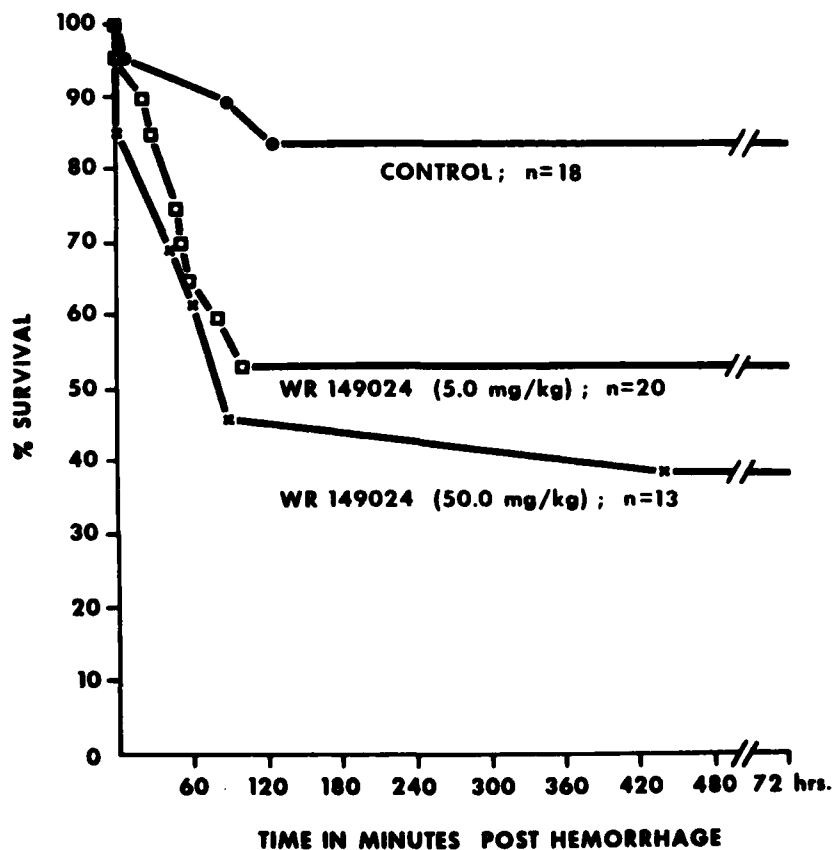


Figure 1. Survival curves illustrating the effect of WR 149024 (5.0 and 50.0 mg/kg, IP) on survival, when administered during hemorrhage. Both WR 149024 treatments are significantly different from the control ($p<0.021$).

DISCUSSION

In 1973, investigators (3) reported that WR 149024, increased survival following hemorrhagic shock and reinfusion of the shed blood. In the present study, we evaluated the effect of WR 149024 on survival following hemorrhage in conscious rats receiving no volume replacement. Both the 5.0 and 50.0 mg/kg doses of WR 149024 produced a significant decrease in survival following hypovolemic shock. These doses are below the LD₅₀ (204 mg/kg) determined for WR 149024 given IP to guinea pigs (5).

Our results dispute the data reported by Caldwell and Demaree (3). However, the hemorrhage model used in the present study and the experiments of Caldwell and Demaree (3) are quite different in design; these authors reinfused shed blood along with WR 149024 and did not withdraw a fixed volume of blood. This disparity in models may account for the discrepancies in the survival data. Furthermore, WR 149024 has been characterized as a general alpha receptor antagonist (1,2). It is expected that an alpha antagonist would cause vasodilatation, an undesirable condition following hemorrhage without volume replacement. Recently, however, Adams (6) has pointed out that nonselective alpha antagonists may increase the availability of catecholamines and thus stimulate beta receptors, resulting in tachycardia and cardiac stimulation associated with general alpha blockers. This condition might possibly mitigate the shock response.

In preliminary studies, 16 mg/kg of WR 149024 given to conscious normal and exsanguinated swine intravenously produced unfavorable hemodynamic changes. Both the normal and hemorrhaged animals experienced substantial decreases in arterial pressure and cardiac output and increases in peripheral vascular resistance--conditions which would be detrimental to tissue perfusion and oxygen delivery. Figure 2 illustrates these hemodynamic parameters from a hemorrhaged pig treated with WR 149024. Caldwell and associates (3,7) reported that, although arterial pressure is reduced following WR 149024 treatment, cardiac output is significantly increased over controls and no change in peripheral vascular resistance was observed. These swine experiments confirm the effect of WR 149024 on arterial pressure but are inconsistent with the cardiac output and vascular resistance data. The evidence presented for rats indicates that the exsanguinated animal has a decreased chance of survival, following WR 149024 treatment of severe hemorrhage.

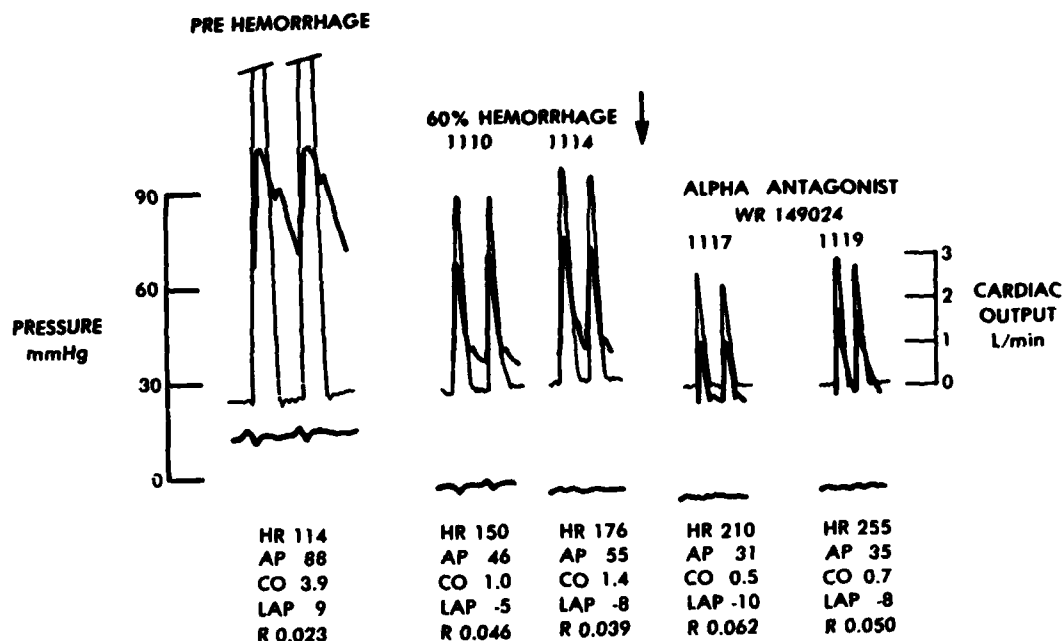


Figure 2. Hemodynamic parameters from an exsanguinated pig (60% of the estimated blood volume removed in 15 minutes) and subsequently treated with WR 149024 (16 mg/kg intravenously) with no reinfusion of blood. HR = heart rate; AP = mean arterial pressure (thick trace); CO = cardiac output (thin trace); LAP = left arterial pressure (bottom trace); R = peripheral vascular resistance. The arrow indicates the injection of WR 149024. The time (a.m.) of each recording posthemorrhage is given about the trace.

CONCLUSION

The data indicate that WR 149024 not only does not improve survival following hemorrhage, when transfusion treatment is unavailable, but also increases the death rate.

RECOMMENDATION

None

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